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A meta-analysis of debulking surgery versus surgical biopsy for unresectable thymoma

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ABSTRACT

Observational studies on long-term outcomes following debulking surgery or surgical biopsy for unresectable thymoma showed various results. This meta-analysis was designed to determine the effect of debulking surgery against surgical biopsy on overall survival in patients with unresectable thymoma. The PubMed database was queried for studies published in the English language on unresectable thymoma and overall survival. We compared overall survival following surgery in patients undergoing debulking surgery and patients undergoing surgical biopsy for unresectable thymoma. Meta-analysis was performed using the Mantel-Haenszel method, and potential publication bias was evaluated with a funnel plot of precision. No randomized trials on this topic were identified. Thirteen retrospective observational studies containing a sum of 314 patients with the number of deaths and person-year information were suitable for analysis. Information on Masaoka stages, World Health Organization histology, and indications for debulking surgery versus surgical biopsy was lacking in most studies. Diversity of neoadjuvant and adjuvant treatments was noted among the eligible studies. One hundred and seventy-two (54.8 %) underwent debulking surgery and 142 (45.2 %) underwent surgical biopsy. The pooled hazard ratio was 0.451 (95% confidence interval: 0.336-0.605, $p < 0.001$), favouring patients undergoing debulking surgery compared with patients undergoing surgical biopsy. The funnel plot of precision demonstrated no important publication bias. Our results suggested that debulking surgery for unresectable thymoma may be associated with improved overall survival and be considered for patients with unresectable thymoma.

Key words: thymoma, biopsy, surgery, survival

INTRODUCTION

Although complete resection of thymoma has been reported as a significant favourable factor of improved overall survival [1-7], a portion of thymectomies for locally advanced thymoma end up with incomplete resection with or without neoadjuvant treatments [8-27]. From a surgical point of view, when faced with apparently unresectable thymoma or one which is deemed impossible to completely resect, for example, due to a number of disseminated nodules or great vessel involvement, in an operating room, thoracic surgeons are required to select from two options; debulking surgery versus surgical biopsy only. Some of previous observational studies suggested a significant difference in overall survival between patients undergoing debulking surgery and those undergoing surgical biopsy only [2,7,10,11,13, 14,16, 20, 22-24], while others did not [1,3-6,9,12,15,17,19]. There is a paucity of published data on the surgical management of unresectable thymoma. Given the absence of high quality evidence and the relatively small sizes of relevant published cohorts, we designed a quantitative meta-analysis to approach this question.

MATERIALS & METHODS

A search of the PubMed database (United States National Library of Medicine) using the terms *thymoma*, *surgery*, *biopsy* and *survival* resulted in 367 articles on 27th of September, 2013. The flow of selecting eligible articles was reported following the PRISMA statement (preferred reporting items for systematic reviews and meta-analysis, Figure 1). The abstracts of these 367 articles were independently reviewed by board-certified thoracic surgeons (M.H and F.K) and, as a result, 133 abstracts, which included patients treated for locally advanced thymic epithelial tumors, were selected for review of full papers. Among the 133 studies, 25 studies which reported overall survival following surgery both for patients undergoing debulking surgery and patients undergoing surgical biopsy for locally advanced, unresectable thymoma were chosen for our review, after excluding the articles which analyzed both debulking surgery and surgical biopsy in the same group and the articles which analyzed only thymic carcinoma or thymic carcinoid. Then three articles

were excluded because overall survival was calculated from the date of adjuvant radiotherapy [1,12] and the date of diagnosis [20], not surgery. Among the 22 studies, which were reviewed by two study statisticians (Sato T and Sozu T), 13 studies from which information on the number of deaths and person-year information can be extracted were finally chosen for a quantitative meta-analysis [2-4,7-14,17,19, 24, 25]. The number of deaths and person-year were extracted from individual patient data in 4 studies and were approximately calculated from Kaplan-Meier plots in 7 studies, the number of deaths was reported and person-years were calculated from mean follow-up years in 1 study, and the number of deaths in five years was reported and person-years were approximately calculated in 1 study (Table 1).

In the analysis of studies with person-year information, we assumed exponential distribution as survival distributions in which the hazard within debulking surgery or surgical biopsy subgroup was constant by time. The combined estimate of the hazard ratio and its confidence interval were calculated by the Mantel-Haenszel method [28]. All confidence intervals are at the 95% level. Heterogeneity among studies was assessed by the I^2 statistics. For the test of heterogeneity, we applied the same idea used in the Breslow-Day test of the odds ratio homogeneity to the Poisson conditional score test. We used JMP 10.0.2 (SAS Institute, Cary, NC) for statistical analysis.

In addition, number of patients in each Masaoka stage and number of patients undergoing neoadjuvant or adjuvant chemotherapy and radiotherapy (or chemotherapy or radiotherapy following surgical biopsy or debulking surgery) in each patient group were extracted for reference but these data were not included in the meta-analysis.

RESULTS

Level of Available Evidence (“Best Evidence”)

No randomized trials comparing debulking surgery and surgical biopsy for unresectable thymoma were found. We identified 13 retrospective cohort studies that described the number of deaths and person-year information following surgery both for patients undergoing debulking surgery and for

patients undergoing surgical biopsy (Table 1). Each of these 13 studies was a retrospective case series representing 8 to 74 patients with unresectable thymoma. A total of 314 patients comprised the study group; 172 (54.8%) underwent debulking surgery and 142 (45.2%) underwent surgical biopsy.

Indications and descriptions for debulking surgery or surgical biopsy of unresectable thymoma.

Selection criteria for patients undergoing debulking surgery or surgical biopsy for unresectable thymoma were not provided in any of the reviewed articles. The definition of debulking surgery was described in two articles as removing 90 % or more of tumor burden [13,14], while not described in the other articles. Debulking surgery was described as subtotal resection in 4 studies (30.8%) [2, 3, 24, 25], as partial resection in 6 studies (46.2%) [7, 9-11, 17, 19], as incomplete resection in one study (7.7%) [4], and as debulking surgery in 2 studies (15.4%) [13, 14].

The approach for surgical debulking and surgical biopsy was specified (as sternotomy or thoracotomy, not mediastinoscopy, in all surgical biopsy patients) in 5 studies (38.5%) [9, 14, 19, 24, 25], while not specified in the rest 8 studies. No minimally invasive approach was described in any article.

Masaoka stage of unresectable thymomas

Masaoka stages of unresectable thymoma in each category patients were available in 4 (30.8%) of the 13 studies (Table 2). Both in debulking surgery or surgical biopsy, there were no patients with Masaoka stage I or II thymoma, but only patients with stage III or stage IV thymoma. Most articles did not provide details on stage III (such as great vessel involvement) were not described, although Froudarakis et al [11] described all of stage III patients undergoing debulking surgery had great vessel involvement and Liu et al [14] described 7 (77.8%) of 9 stage III patients undergoing debulking surgery had great vessel involvement.

Neoadjuvant or adjuvant treatments (chemotherapy and radiotherapy)

Data or description on the numbers of patients undergoing neoadjuvant chemotherapy and radiotherapy were available only in one study [4]. Data on the use of chemotherapy and/or radiotherapy following debulking surgery and surgical biopsy were available in 9 of the 13 studies (Table 3). Postoperative (adjuvant) radiotherapy was performed in 75-100 % (a median of 85.8%) of patients undergoing debulking surgery and 25-100 % (a median of 87.5%) of patients undergoing surgical biopsy, while (adjuvant) chemotherapy was performed in 14.3-42.9 % (a median of 27.5%) of patients undergoing debulking surgery and 25-75 % (a median of 47.8%) of patients undergoing surgical biopsy.

Comparison of postoperative mortality and overall survival between patients undergoing debulking surgery and surgical biopsy for unresectable thymoma

Postoperative mortality (within 30 days) was 0% for both debulking surgery and surgical biopsy in 5 studies [4, 9, 10, 11, 19], and it was not available for each group in 6 studies [2, 7, 14, 17, 24, 25]. It was 0% for debulking surgery but 14.3% for surgical biopsy in 1 study [3] and 0% for debulking surgery and 9.1% for surgical biopsy in 1 study [13].

Results of the quantitative meta-analysis for the 13 studies describing the number of deaths and person-year information following surgery (debulking surgery or surgical biopsy) were shown in Figure 2. As shown in Table 1, information on the number of deaths and person-years were extracted from 13 studies. Six of the 13 individual studies showed statistically significant hazard ratios favouring debulking surgery for unresectable thymoma compared with surgical biopsy. The pooled hazard ratio using the Mantel-Haenszel method was 0.451 (95% confidence interval: 0.336-0.605, $P < 0.001$).

Five-year overall survival rate by Kaplan-Meier method ranged from 16% to 100%, with a median of 64% in patients undergoing debulking surgery, while the rate ranged from 0% to 66.7%,

with a median of 35% in patients undergoing surgical biopsy.

Publication bias and/or heterogeneity of results reported in each individual study

Figure 3 shows a funnel plot of precision by log hazard ratio for the 13 studies describing the number of deaths and person-year information following surgery (debulking surgery or surgical biopsy). The plot showed that all the studies fall within the funnel and most are centered on the median axis, suggesting a lack of important publication bias. $I^2=58\%$ showed a moderate heterogeneity among 13 included studies.

DISCUSSION

Given the overall incidence of thymoma and its relatively indolent biologic behaviour, the current dearth of data on the management of unresectable thymoma is not surprising. These same factors essentially preclude organization of a randomized controlled trial on the treatment of unresectable thymoma patients. Our current knowledge of this problem is derived exclusively from level 3 evidence in the form of retrospective case series, and there have been no prospective studies focusing on this patient population. We therefore designed a quantitative meta-analysis to explore the utility of debulking surgery against surgical biopsy in this group of patients.

Our meta-analysis was constructed from 13 studies published from 1981 to 2006 and represented 314 patients treated for unresectable thymoma in the United States, Japan, China, Spain, Greece, Taiwan, and Italy [2-4, 7-14, 17, 19, 24, 25]. The results of our quantitative meta-analysis demonstrated that patients undergoing debulking surgery for unresectable thymoma had improved overall survival compared to patients undergoing surgical biopsy. All surgical biopsies were performed via sternotomy or thoracotomy in the 5 studies describing the approach in this meta-analysis. With respect to high diagnostic yield (80-100%) of recent image guided percutaneous techniques of mediastinal mass [29, 30], it may be reasonable to consider more than diagnostic procedures once sternotomy or thoracotomy is performed.

The role of multimodality therapy in the management of unresectable thymoma could not be

fully evaluated in this study because the only description on neoadjuvant treatments for both groups was available in the article of Rea et al [4] and no neoadjuvant treatments apparently were performed in the other 12 studies. Neoadjuvant chemotherapy or chemoradiotherapy followed by surgery may be promising treatment modalities for locally advanced unresectable thymoma, but the long-term outcomes are pending [31,32].

It should be noted that patients in the included studies underwent debulking surgery versus surgical biopsy, followed by (adjuvant) radiotherapy and/or by chemotherapy. Although statistical analysis was not performed, radiotherapy appeared to be performed frequently following both debulking surgery and surgical biopsy and to be performed more frequently than chemotherapy. Adjuvant chemotherapy apparently was performed more frequently in patients undergoing surgical biopsy than those undergoing debulking surgery in our study. As pointed out in several studies [3, 13, 14], adjuvant radiotherapy may improve overall survival following debulking surgery or surgical biopsy for locally advanced unresectable thymoma. Adjuvant chemotherapy has been less discussed and performed than radiotherapy as an adjuvant treatment, but may be considered following debulking surgery [26]. Given that except for the 13 included studies, there have been only a few articles on patients undergoing radiotherapy only, chemotherapy only or chemoradiotherapy only [33-35], this meta-analysis is noted for investigating debulking surgery versus biopsy only prior to chemotherapy, radiotherapy, or chemoradiotherapy. The superiority of debulking surgery over surgical biopsy in this meta-analysis should be understood in the setting of frequent postoperative treatments.

Meta-analyses are useful tools for the evaluation of rare populations such as ours, but they are inherently constrained by the limitations of the original studies from which they are comprised. In addition, a meta-analysis of retrospective cohort studies included another limitation: hazard ratio of a treatment to the other in overall survival is rarely described or available. Several studies other than 13 eligible studies were excluded because they reported only 5 year or 10 year overall survival rates and did not help estimate hazard ratio in overall survival, while Kaplan-Meier curves in 7 studies in

our meta-analysis were helpful in estimating the number of death and person-year information.

Although I^2 of 58% in our meta-analysis suggested a moderate heterogeneity, but debulking surgery is still considered favorable because only 3 studies [9, 11, 19] showed more than 1 of hazard ratio (debulking surgery unfavorable) in the forest plot. Our funnel plot analyses did not demonstrate an important relationship between treatment effect and study size, and therefore suggested the absence of important publication bias.

Our meta-analysis demonstrates improved overall survival in patients operated on with radical intents undergoing debulking surgery for unresectable thymoma, compared to those undergoing surgical biopsy. Although selection biases were present in each of the original studies in our meta-analysis, the improved overall survival in the debulking group suggests a consideration of aggressive debulking in patients with unresectable thymoma unless preoperative workup shows too extensive diseases such as multiple vascular involvement or numerous pleural implants.

Since neoadjuvant treatments could not be evaluated in this meta-analysis, a potential future analysis will be to investigate the effect of debulking surgery following neoadjuvant chemotherapy or chemoradiotherapy on long-term outcomes in locally advanced (presumably unresectable at presentation) thymomas.

TABLES

Table 1. Characteristics of the individual studies which were selected for a quantitative meta-analysis.

Study	year	total (N)	debulking (N)	5y OS	biopsy (N)	5y OS	*Information extracted
Chahinian et al [9]	1981	8	4	50%	4	0%	a
Masaoka et al [3]	1981	20	13	69.2%	7	57.1%	a
Cohen et al [19]	1984	10	7	14.3%	3	66.7%	b
Maggi et al [24]	1991	30	21	71.7%	9	40%	c
Wang L [17]	1992	27	9	40%	18	45%	c
Egea et al [10]	1995	11	7	15%	4	0%	c
Froudarakis et al [11]	2001	15	3	100%	12	8.3%	a
Rios et al [7]	2002	14	10	50%	4	0%	c
Kondo et al [2]	2003	74	50	64.4%	24	35.6%	c
Wang Y et al [25]	2003	20	14	66.4%	6	16.7%	d
Lin et al [13]	2004	18	7	85%	11	45%	a
Rea et al [4]	2004	24	12	16%	12	33%	c
Liu et al [14]	2006	43	15	71%	28	35%	c

OS; overall survival, ND; no data, RT; radiotherapy, KM; Kaplan-Meier

*Information extracted

- Number of deaths and person-years were calculated from individual data.
- Number of deaths was reported and person-years were calculated from mean follow-up years.
- Number of deaths and person-years were approximately calculated from Kaplan-Meier plots.
- Number of deaths in five years was reported and person-years were approximately calculated.

Table 2. Masaoka stages at surgery in patients undergoing debulking surgery and those undergoing surgical biopsy.

Study	year	Total (N)	debulking (N)	stage III	stage IV	biopsy (N)	stage III	stage IV
<hr/>								
Masaoka et al [3]	1981	20	13	5	A; 6	7	4	A; 2 (28.6%)
				(38.4%)	B; 2		(57.1%)	B; 1 (14.3%)
				(15.4%)				
Froudarakis et al [11]	2001	15	3	3 (20%)	0	12	3 (25%)	9 (75%)
Lin et al [13]	2004	18	7	5 (71.4%)	A; 2 (28.6%)	11	7 (63.6%)	A; 4 (36.4%)
Liu et al [14]	2006	43	15	9 (60%)	A; 6 (40%)	28	13 (46.4%)	A; 15 (53.6%)
<hr/>								
ND; no data								

Table 3. Number of patients undergoing chemotherapy and/or radiotherapy following debulking surgery or surgical biopsy.

Study	year	Total (N)	Chemo in all	RT in all	debulking (N)	Chemo	RT	biopsy (N)	Chemo	RT
Chahinian et al [9]	1981	8	0	6 (75%)	4	0	3 (75%)	4	1 (25%)	3 (75%)
Masaoka et al [3]	1981	20	8 (38.2%)	17 (80.9%)	13	4 (30.8%)	11 (84.6%)	7	4 (57.1%)	6 (85.7%)
Cohen et al [19]	1984	10	2 (20%)	9 (90%)	7	1 (14.3%)	6 (85.7%)	3	1 (33%)	3 (100%)
Wang L [17]	1992	27	7 (25.9%)	ND	9	2 (22.2%)	ND	18	5 (27.8%)	ND
Froudarakis et al [11]	2001	15	10 (66.7%)	6 (40%)	3	1 (33.3%)	3 (100%)	12	9 (75%)	3 (25%)
Rios et al [7]	2002	14	ND	14 (100%)	10	ND	10 (100%)	4	ND	4 (100%)
Lin et al [13]	2004	18	9 (50%)	16 (88.9%)	7	3 (42.9%)	6 (85.8%)	11	5 (45.6%)	10 (90%)

						%)	%)			
Rea et al [4]	2004	24	24 (100%)	24 (100%)	12	ND	ND	12	ND	ND
Liu et al [14]	2006	43	19 (44.2%)	33 (76.8%)	15	ND	ND	28	ND	ND

Chemo; chemotherapy, RT; radiotherapy, ND; no data

Figure legends

Figure 1. The flow of selecting eligible papers following PRISMA (preferred reporting items for systematic reviews and meta-analysis) statement.

Figure 2. Comparisons of overall survival following surgery in patients treated with debulking surgery and surgical biopsy, with meta-analysis using Mantel-Haenszel method. The left portions of the figure show the studies analyzed with their corresponding hazard ratio, lower and upper limits, and P value. The right portions of the figure show a forest plot of the data. The horizontal lines represent the values within the 95% confidence interval (CI) of the underlying effects. The vertical line indicates a hazard ratio of 1.

Figure 3. A funnel plot of precision by log hazard ratio showed that all the studies fall almost symmetrically and most are centered on the median axis, suggesting a lack of important publication bias.

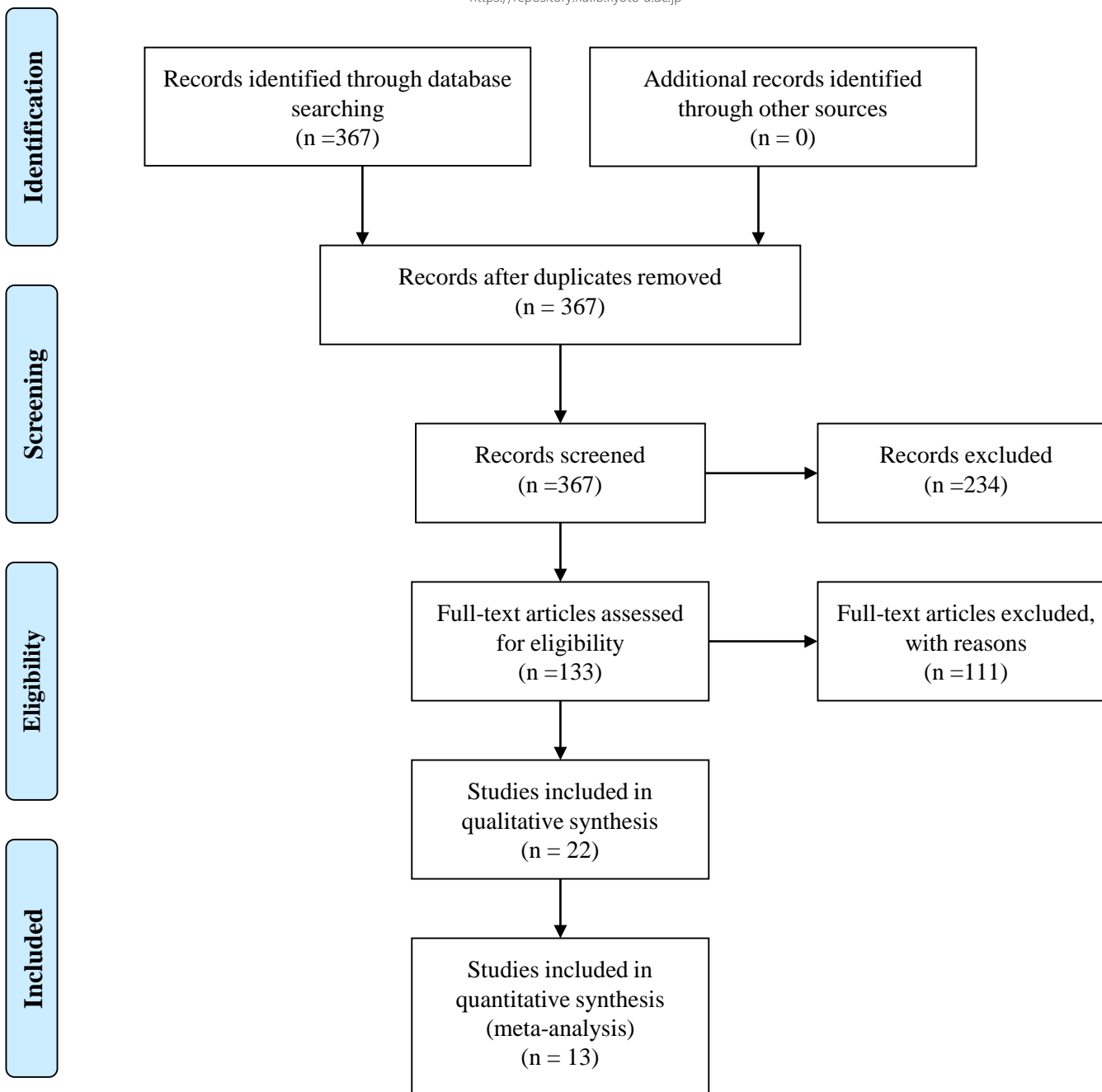
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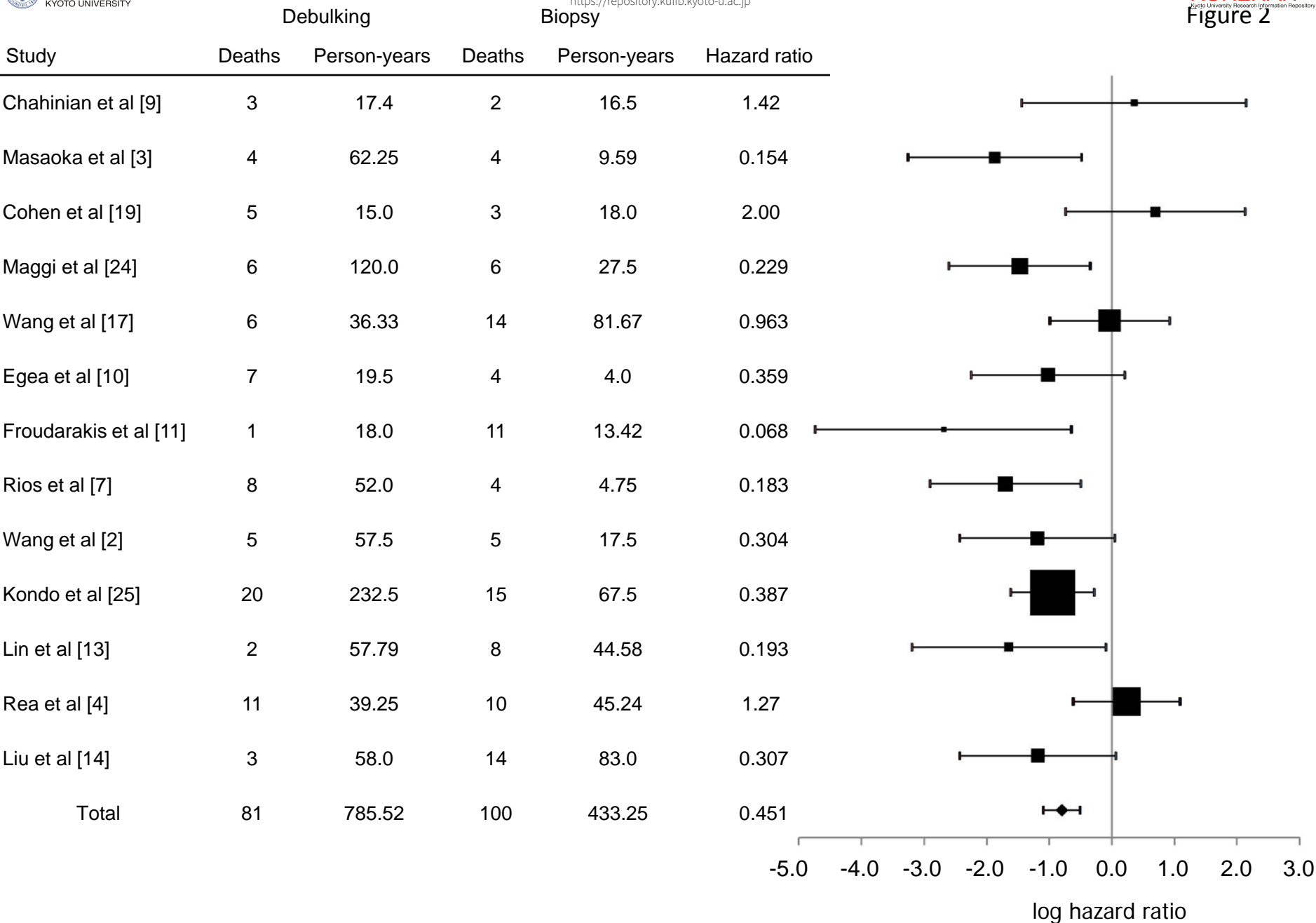




Figure 3

